REMARKS

A. Claim Amendments

Claim 2 has been amended to that the cleavage of soluble TNFα from native TNFα and TNFα lacking the metalloproteinase cleavage site present from the valine 77 to the proline 88 of native TNFα is as it can be measured in the recited cell lines, support for which is found in, for example, the text of the Specification spanning paragraph 0111 to 0113, and Figures 3 through 5.

Claims 3, 4 and 11 have been amended so the wording of each corresponds to the antecedent basis provided by Claim 2, from which each depends.

Claim 8 has been cancelled as redundant of Claim 2.

Claim 76 has been amended so the wording thereof conforms to that of paragraph 0078 of the Specification.

No new matter has been added to the application by the amendment and newly added claims, entry of which is therefore respectfully requested.

B. Response to Rejection of Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 under 35 USC Section 103(a)

The claims are rejected as obvious over Kipps, *et al.* US Patent No. 7,070,771 (and/or the same disclosure of Kipps, *et al.*, WO 98/26061), in view of Mueller, *et al.*, *J.Biol.Chem.*, 274:38112-38118, 1999 and Kornbluth (US2005/0158831). This rejection is maintained from the previous Office Action.

The claimed invention is directed to a chimeric molecule consisting of a Domain III element of CD154 from which an mmp cleavage site has been removed and a Domain IV element of TNFα from which an mmp cleavage site has been removed, *wherein* the molecule produces less cleaved, soluble TNFα than does a non-chimeric TNFα from which the same cleavage site in Domain IV has been removed (e.g., the molecule described in the cited Mueller reference). The purpose in avoiding the release of soluble TNFα from cell membranes is to limit the molecule's range of activities to its immunostimulatory function (Specification at paragraphs 0008-0009).

Applicants submit that the combination of references relied upon for the present rejection fail to render the claimed invention obvious for at least three reasons: (1) the references fail to teach or chimeric molecule having the specific structure now claimed; (2) the Kornbluth reference teaches away from the invention by providing CD154-collectin chimera in which (i) mmp cleavage of CD154 is *desirable* (see, e.g., paragraph 0090) and (ii) only the *collectin* component is modified (see, paragraphs 0091, 0098, 0103 and SEQ.ID.No. 1 [deletion of CRD site from collectin]); and (3) the references fail to teach or suggest an effect for removal of an mmp site from Domain III of CD154 as to any impact of combining such a modified CD154 Domain III with an mmp-deleted TNFα Domain IV on production of soluble TNFα.

As to the latter point, the Office Action avers (at page 7, 8th paragraph) that the 'relative cleavage of the soluble TNF molecule was cell-line dependent...and the claims are <u>not</u> limited to any particular cell line." (emphasis in original). While Applicants do not agree with the conclusion that the reduction of soluble TNF production from the claimed chimera is as cell line dependent as the Office Action suggests, the claims have nonetheless been amended to identify a cell line in which such a reduction is established by the specification (see, paragraphs 0111 to 0113 of the Specification). Therefore, the claims now clearly define the standard of reduced solubility against which the claimed molecule is measured.

As to the references' failure to teach the structure of the claimed molecules, the Office Action asserts that the task of identifying cleavage sites whose removal from a molecule would impact its solubility is rendered straightforward by the cited combination of references. Applicants strongly disagree.

Mueller describes only a full-length, non-chimeric TNFα molecule from which a mmp site was removed. Mueller makes it quite clear that removal of that mmp site alone was not sufficient to mitigate release of TNFα (sTNFα), which was still be found at significant levels in the cell supernatants (see, e.g., Figure 2B, lane 5, at Mueller, *et al.,* page 38114, and Specification at paragraph 007). Thus, Mueller did not guide the way to creation of the molecules of the invention, which provide a chimeric TNFα that is, by the explicit terms of the present claims, more resistant to cleavage than the molecule described by Mueller, *et al.*

Kipps, *et al.* is similarly lacking in guidance, in that nothing in the reference points the art to any means for resisting cleavage of TNFα. Instead, the focus of the reference is on providing molecules that are capable of expression in cells in which expression might otherwise be lacking; e.g., for antigen presentation of the disclosed chimera (see, e.g., Col. 3, line 66 to Col. 4, line 19). Known mmp cleavage sites are identified in Kipps, et al.'s Figure 28, but the reference does not point to the removal of any such sites to reduce production of soluble TNFα.

Taken together, therefore, Kipps, et al. and Mueller, et al. can at most be read to suggest the concept that removing mmp cleavage sites from a portion of a TNFα molecule (possibly including a chimeric molecule) might reduce sTNFα production to the limited degree observed by Mueller, *et al.* Neither reference points to the effect of combining such a modified TNFα molecule with any CD154 domain fragment that itself lacks an mmp cleavage site.

Nevertheless, the Office Action asserts that the addition of the Kornbluth reference to the cited combination provides the art with motivation to make chimeric molecules in which the CD154 element lacks a mmp cleavage site. Applicants previously responded that Kornbluth actually teaches away from the claimed invention by focusing on *providing for release of soluble fusion protein from cell* membranes to mimic, not avoid, the effect of soluble CD154:

> The present invention contemplates a method of preparing soluble, multimeric mammalian proteins by culturing a host cell transformed or transfected with an expression vector encoding a fusion protein comprising the hub, body, and neck region of a collectin molecule and a heterologous mammalian protein [CD154].
>
> (Kornbluth, paragraph 0013)
>
> Because of the multimeric nature of the collectin backbone, such fusion proteins may **mimic** the multivalent ligand surface presented by the membrane forms of TNFSF members to TNFRSF-bearing responding cells.
>
> (*ibid.,* paragraph 0101, emphasis added)

The result is a soluble CD154 molecule that is stable when cleaved from a cell membrane and retains its full "range of activities" as compared to the native CD154 molecule (paragraph 0066 "while remaining soluble, CD40L-SPD equals CD40L in its range of activities").

To the extent that any modification of the fusion protein is made to affect cleavage, it is to minimize cleavage of the collectin component and the CD154 from one another, *not* from the cell membrane. To that end, the CRD site of collectin, on which mmp*s* whose release is stimulated by CD154, is removed:

> ...multimeric TNFSF-SPD fusion protein having a plurality of polypeptide trimers, a first trimer consisting of peptide strands of members of the TNF superfamily (TNFSF) of ligands, and a second trimer strand from a collectin molecule, each first trimer conjoined to a second polypeptide trimer strand from a collectin molecule, wherein said ligand strand is substituted for native carbohydrate recognition domains (CRD) of the collectin molecules.
>
> (Kornbluth, paragraph 20)
>
> ...Additionally, metalloproteinases are known to degrade the collectin, C1q, so that a fusion with C1q may alter the degradation of the fusion protein. For example, because CD40L activates macrophages and other cells to produce metalloproteinases, which could potentially degrade the collagenous portion of SPD [CRD] and other collecting [*sic*].
>
> (paragraph 0098).

The result is ostensibly a CD154-collectin (SPD) molecule that is internally stable (the trimer strands don't cleave from one another) but is released in soluble form from cell membranes at full activity (paragraphs 0008-0010, 0013 and 0066).

In direct contrast, the invention focuses on *retaining* of CD154-TNFα on cell membranes, to avoid release of soluble TNFα, and limit its activity. Nonetheless, the Office Action contends that one of ordinary skill in the art would find reason to combine Kornbluth's teaching regarding *increasing* production of one soluble molecule with Mueller's teaching regarding *reducing* solubility of another. Somehow, from that basis, one in the art ostensibly is able to identify which of the 162 species of chimeric molecules described by Kipps *et al.* may be modified in a way not suggested by either Kornbluth or Mueller to result in the claimed molecules, with reduced solubility greater than that observed by Mueller.

Only with the hindsight benefit of the present disclosure would such a leap of imagination be possible. Yet, even if one were to defy logic by combining references that lead to opposite outcomes, a careful reading of the references reveals that doing so would not offer any guidance regarding removing an mmp site from a CD154 Domain III component of an mmp-deleted TNFα chimeric molecule to prevent release of the soluble form of the latter molecule. To the contrary, any inclination to so tinker with molecules is discouraged by Kornbluth, who cautions that the impact of such changes be unpredictable (Paragraph 0098)[1]. With such a warning in hand, the artisan is left with no motivation or guidance to select the specific CD154-TNFα construct claimed as one from which release of soluble TNFα from cell membranes could be eliminated.

In summary, Mueller discusses a lesser reduction in soluble TNFα production through removal of its mmp site but *says nothing about CD154*, while Kipps et al. *mentions CD154 but says nothing about modifying it* for combination with a modified TNFα molecule to reduce the latter's cleavage from cell membranes, and Kornbluth *points one to modifications a different molecule* (a collectin) for an opposite purpose. This combination of references therefore neither teaches nor suggests the claimed invention; i.e., a CD154- TNFα in which both elements have been modified by removal of mmp sites to virtually eliminate soluble TNFα production.

Based on all of the foregoing, as well as Applicants' previous arguments of record, Applicants respectfully submit that the invention of the pending claims is not obvious over Kipps, *et al.*, in view of Mueller, *et al.* and Kornbluth. Reconsideration and withdrawal of the claims rejection under 35 USC §103 is therefore requested.

[1] "Accordingly, it would be expected that collectins other than SPD might confer different cell-binding and pharmacokinetic behaviors upon a fusion protein. For example, macrophages are known to take up and degrade whole SPD...[i]f a fusion protein other than SPD were used, the disposition of the fusion protein might be altered."

C. Response to Rejection of Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 under 35 USC 112, First Paragraph (new matter).

The listed claims are rejected on the basis that "the Domain III comprises a CD154 fragment lacking a metalloproteinase cleavage site present in wild-type CD154" limitation included lacks support in the Specification for "CD154 fragment lacking a metalloproteinase cleavage site" and "wild-type CD154", and is therefore new matter. Applicants respectfully disagree.

Claim 1 has been amended to clarify that it is an mmp cleavage site from Domain III of CD154 that is the subject of the limitation at issue. Such a modified CD154 Domain III is described in the application at, for example, paragraph 0086 (and is detailed in SEQ.ID.No. 1). The 'wild-type' reference is implicit in the application (in that domains of CD154 are described and their sequence provided (see, e.g., SEQ.ID.No. 5), but the claim has been amended for purposes of expediting allowance. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

D. Response to Rejection of Claims 2-4, 8, 11-12, 27-29, 32-41, 68 and 76-79 under 35 USC 112, First Paragraph (written description).

The listed claims are rejected on the basis that "the Domain III comprises a CD154 fragment lacking a metalloproteinase cleavage site present in wild-type CD154" limitation and the "than are native TNFα and TNFα lacking a mmp cleavage site between Val77 and Pro88 of native TNFα" lack support in the Specification. Applicants respectfully disagree.

As to the word 'fragment' in the "...Domain III comprises a CD154 fragment..." limitation, the concept is clearly defined by the claim as written—the fragment is the portion of CD154 Domain III remaining after removal of the recited mmp cleavage site. Nonetheless, to expedite allowance, the claim has been amended to remove the word fragment as redundant.

As to the definition of 'native TNFα" and the amino acids removed from Domain IV thereof, this portion of the construct is clearly defined in the Specification. For example, in paragraph 0078 identifies a native TNFα as the *pre-cleavage* molecule which, when cleaved, results in release of soluble TNFα:

> [078] As used herein, the phrase "less susceptible to cleavage" refers to the higher resistance of a chimeric TNFα to proteolytic cleavage compared to that of native TNFα, as measured by the amount of soluble TNF generated by a given number of cells over a period of time. Thus, a chimeric TNFα of the present invention is "less susceptible to cleavage" because it is cleaved at a rate preferably at least 90% less than that of native TNFα.

The claimed molecules are 'less susceptible to cleavage' than both native TNFα and the mmp-deleted TNFα which lacks the portion of Domain III lying between Val77 and Pro88; i.e., the molecule described by Mueller and in the Specification at paragraph 0082:

> [082] According to the invention, domain III of TNFα includes sequences of amino acids that are cleaved by proteases. For instance, cleavage sites have been identified for TNFα between amino acids ALA76 and VAL77. Cleavage at this site generates a soluble form of the TNFα molecule. As noted above, native TNFα may have additional cleavage sites in domains I-IV(Mueller et al, J Biol Chem, 274:38112-38118, 1999).

The rate of soluble TNFα production from native TNFα is known in the art and described in the Specification at paragraphs 0033, 0111, 0112 and the unnumbered paragraph which follows paragraph 0112 at page 33, as well as Figures 3 through 5. The rate of soluble TNFα production from the TNFα which lacks the portion of Domain III lying between Val77 and Pro88 is described by Mueller and in paragraphs 0082 and 0116 of the Specification. The reduced cleavage of TNFα from the claimed chimera as compared to the recited reference molecules is demonstrated in the Specification at, for example, paragraphs 0111, 0112, and the unnumbered paragraph which follows paragraph 0112 at page 33, as well as Figures 3 through 5 (see, references to CD154:TNF, the presently claimed construct.

The claim limitations at issue are therefore clearly supported by the written description provided by the application. Reconsideration and withdrawal of the rejection is therefore respectfully requested.

E. Response to the Double-Patenting Rejection

The rejection of claims 2-4, 8, 11-12, 27-29, 32-41, 68, and 76-79 on the ground of obviousness-type double patenting as allegedly being unpatentable over claims 66 and 68-75 of USSN 11/015,117 (now U.S. Patent No. 7,524,944; hereinafter "the '944 patent") to Kipps *et al.* is respectfully traversed.

While not acquiescing to the substantive basis for this rejection, in order to reduce the issues and expedite prosecution, a terminal disclaimer over the commonly-owned '944 patent is submitted herewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 2-4, 8, 11-12, 27-29, 32-41, 68, and 76-79 on the ground of obviousness-type double patenting as allegedly being unpatentable over claims 1-15 of U.S. Patent No. 7,070,771 (hereinafter "the '771 patent") to Kipps *et al.* and claims 1-17 of U.S. Patent No. 7,495,090 (hereinafter "the '090 patent") to Prussak *et al.* is respectfully traversed.

While not acquiescing to the substantive basis for this rejection, in order to reduce the issues and expedite prosecution, a terminal disclaimer over the commonly-owned '771 patent and a terminal disclaimer over the commonly-owned '090 patent are submitted herewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

The rejection of claims 2-4, 8, 11-12, 27-29, 32-41, 68, and 76-79 on the ground of obviousness-type double patenting as allegedly being unpatentable over claims 66 and 68-75 of USSN 11/015,117 (now U.S. Patent No. 7,524,944; hereinafter "the '944 patent") to Kipps *et al.* and over claims 1-15 of U.S. Patent No. 7,070,771 (hereinafter "the '771 patent") to Kipps *et al.* is respectfully traversed.

While not acquiescing to the substantive basis for this rejection, in order to reduce the issues and expedite prosecution, a terminal disclaimer over the commonly-owned '944 patent and a terminal disclaimer over the commonly-owned '771 patent are submitted herewith. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

Applicants believe that the present application is now in condition for allowance. Favorable consideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge the total amount of $275.00 as payment for the Petition for One-Month Extension of Time ($65.00) and the Terminal Disclaimer fee (for three Terminal Disclaimers) ($210.00), small entity, to Deposit Account No. 07-1896. No other fee is deemed necessary in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees that may be due in connection with the filing of this paper, or credit any overpayment to Deposit Account No. 07-1896.

Respectfully submitted,

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Attachments: Terminal Disclaimer over U.S. Patent No. 7,070,771
Terminal Disclaimer over U.S. Patent No. 7,495,090
Terminal Disclaimer over U.S. Patent No. 7,524,944